

## CASE REPORT

# Difficulty with learning of exercise instructions associated with 'working memory' dysfunction and frontal glucose hypometabolism in a patient with very mild subcortical vascular dementia with knee osteoarthritis

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## SUMMARY

We present a patient with no dementia, depression or apathy, who had difficulty in learning self-exercise instructions. The patient was an 80-year-old right-handed woman who was admitted to a rehabilitation unit to receive postoperative rehabilitation after a femoral neck fracture. She was instructed quadriceps isometric exercises to perform 10 repetitions and to hold each stretch for 10 s. She performed the exercise correctly with motivation, but she had difficulty in learning the number of repetitions and the duration of each stretch. She had no history of cerebrovascular accident and the neurological examination was normal. Neuropsychological testing, MRI and  $^{18}\text{F}$ -fluoro-D-glucose-positron emission tomography (FDG-PET) were performed to examine the neural mechanisms associated with this difficulty in learning instructions. Neuropsychological tests revealed dysfunction of working memory while other cognitive domains were relatively preserved. Her neuropsychological tests scores were (1) Mini-Mental State Examination: 24 (mild cognitive impairment), (2) Geriatric Depression Scale-15: 2 (no depression), (3) Apathy Scale: 2 (no apathy), (4) digit span forward: 5 (normal), (5) digit span backward: 2 (impaired), (6) visuospatial span forward: 4 (normal), (7) visuospatial span backward: 2 (impaired), (8) frontal assessment battery: 11 (normal), (9) Weigl test: 0 (impaired), (10) trail making test A: 52 s (normal), (11) train making test B: failed (impaired). T2-weighted and fluid-attenuated inversion recovery MRI showed high signal-intensity lesions in the cerebral deep white matter. FDG-PET revealed hypometabolic areas in the bilateral frontal lobes, particularly in the bilateral dorsolateral frontal area, anterior cingulate cortex and orbitofrontal cortex. One of the possible neural mechanisms underlying the learning difficulties in this patient may have been partial blockage of the cingulofrontal network by deep white matter lesions.

## BACKGROUND

Motor learning is a key to a successful outcome of physical therapy. If a patient acquires declarative memory of instructions on procedures for motor learning, efficient physical therapy can be performed. A patient who understands and remembers the contents of home exercise instructions given by a therapist and correctly exercises is likely to maintain or

improve physical functions. For instance, a home exercise programme, including muscle strengthening, muscle stretching and active range of motion exercises, is effective for improving function and decreasing stiffness and pain in patients with osteoarthritis of the knee.<sup>1</sup>

With ageing of the population, many elderly patients require physical therapy. Bone and joint diseases are the commonest diseases causing subsequent dependence in activities of daily living, and rehabilitation therapy plays an important role in treatment.<sup>2</sup>

Neuropsychological inhibitors of physical therapy include dementia,<sup>3</sup> depression<sup>4</sup> and apathy.<sup>5</sup> In addition to general cognitive impairment, explicit motor learning may inhibit physical therapy, linked to various domains, including memory, executive function, etc. However, it is unknown which domain is impaired in patients with disability of learning explicit instructions.

We experienced a patient transferred to our hospital for rehabilitation after surgery for trochanteric fracture complicated with knee osteoarthritis. She was given instructions on isometric contraction exercise of the quadriceps for improvement of gait performance, but she did not remember these instructions, although she did not have dementia, depression or apathy. Therefore, we studied the neuropsychological characteristics and neurological background, using neuropsychological tests, head MRI and  $^{18}\text{F}$ -fluoro-D-glucose-positron emission tomography (FDG-PET).

## CASE PRESENTATION

The patient was an 80-year-old right-handed woman with 8 years of education. She had suffered a left femoral neck fracture and had left knee osteoarthritis. She lived with her husband, who had suffered a stroke, and took care of him and did their housework independently. She had a mild and nervous personality. She had a history of hypertension that had been well controlled by medication for 10 years, but no history of cerebrovascular accident. She had suffered pain in her left knee due to osteoarthritis for 5 years.

Four weeks earlier, she had fallen and sustained a fracture of the left femoral neck. She was admitted to the emergency department in the hospital and

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was treated with osteosynthesis on that day. Her ability to walk gradually improved as her left hip pain improved, and she progressed to walking with a cane at 4 weeks postoperatively. However, her gait was still imbalanced due to postoperative disability and left knee pain, which deteriorated after the operation. Therefore, she transferred to our hospital for further improvement.

A general physical examination revealed no abnormal findings. Her blood pressure was controlled. There were no abnormal findings in neurological examinations and her consciousness was alert. Regarding verbal memory, the patient remembered the episode of the fall and the names of people who she met on a daily basis. In visual memory, she remembered the faces of people who she met on a daily basis, and the locations of the toilet and her bedroom in the rehabilitation ward. She was oriented to time and place, and she had no apraxia and no impairments in language, attention, visuospatial function and executive function. Her behaviour caused no difficulties in her daily life, and she was polite, amiable and motivated in her rehabilitation.

Based on the Diagnostic and Statistical Manual of Mental Disorders-IV criteria, a board-certified neurologist (KM) and a geriatrician (Hiroshi Ishii examined her and found no apparent dementia or depression or apathy. However, taking her MRI findings into consideration, she met the criteria for very mild stage of subcortical vascular dementia.<sup>6</sup> Her Mini-Mental State Examination (MMSE) score was 24. Screening for depression was performed using the 15-item Geriatric Depression Scale,<sup>7</sup> on which a value  $\geq 5$  indicates clinically depressive. She obtained a score of 2. Apathy was evaluated on the Apathy Scale consisting of 14 items, on which a value  $\geq 16$  indicates clinical apathy.<sup>8</sup> Her score was 2. Therefore, she had no apparent dementia, depression or apathy. However, she had scores of 1 on subtests of serial 7s.

## INVESTIGATIONS

### Instructions for quadriceps exercise

The patient was instructed to press the back of knee against a rolled towel while trying not to lift her heel off the bed while in the supine position,<sup>9</sup> to hold the muscles tightly contracted for a count of 10, then relax and to repeat this exercise 10 times. Immediately after the first instruction, she was able to perform precisely. She was then asked to learn the exercise instructions to allow the exercise to be performed at home after discharge to control knee pain.

In the next rehabilitation session, the patient was asked by the therapist about the procedure of quadriceps isometric exercises

before the exercise was performed, with a question such as 'Explain the exercise using the towel.' She could demonstrate the action of pushing down on the towel with her knee, but gave the wrong numbers for the counts during pushing down and for repetitions. Therefore, the therapist asked her to recall the exercise instructions at the beginning of every session (at least once a day) until she could remember the right numbers. The exercise was performed at least once a day in the morning or afternoon, and sometimes twice a day. The patient required 14 days before she was able to give the correct numbers in the instructions.

### Course of learning

To compare with this case, we recorded the learning process in other patients without dementia as a control. Clinical data for eight controls aged  $79.5 \pm 8.6$  years are shown in table 1.

They underwent surgery for disorders of bones or joints of the lower extremities and were given the same instructions. None of them showed marked impairment (mean MMSE=25.0) nor met the criteria for depression or apathy. Step-by-step progresses in motor learning are shown in figure 1. The controls achieved memory of motor learning in  $4.0 \pm 1.2$  days, whereas the patient needed 14 days to remember the instructions. The patient walked by herself with a straight cane because of a pain relief and was discharged 8 weeks after she was transferred to the rehabilitation unit of our hospital.

### Physical therapies that did and did not require time for motor learning

The patient underwent other physiotherapy exercises. She was instructed to remember the contents of three kinds of exercises: 'exercise of legs on the bed', 'side walk between parallel bars' and 'stair-stepping exercise'.

The 'exercise of legs on the bed' consisted of lifting the legs in the supine position, rotating the hip joint in the lateral position and extending the hip joint in the prone position, and was performed to increase muscle strength. This exercise was repeated 10 times to provide the patient with an appropriate load in self-exercise. She was asked to remember the number of repeats, and was able to recall this number and answer by rote at the beginning of the next or subsequence sessions.

The 'side walk between parallel bars' involved sideways walking holding parallel bars with both hands, with the goal of improving the gluteus medius. To effectively train this muscle, it is necessary to exercise while keeping the toes straight ahead at a right angle to the parallel bars. Therefore, the patient was asked to remember 'to keep your toes straight ahead'. She was

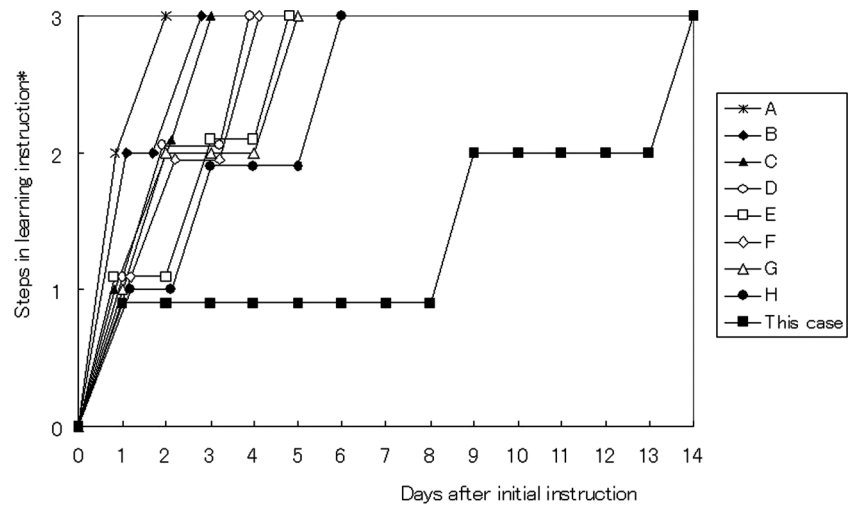
**Table 1** Background information for controls

Patient	Age (years)	Gender	Education (years)	MMSE	Diagnosis	GDS-15	Apathy Scale
A	61	Female	12	29	Left hip fracture after surgery	0	1
B	75	Female	8	26	Right patellar fracture after surgery	1	2
C	77	Female	8	26	Right tibial diaphyseal fracture after surgery	1	4
D	83	Male	8	25	Right hip fracture after surgery	1	3
E	81	Female	9	24	Right hip osteoarthritis after surgery	4	12
F	93	Female	8	24	Right trochanteric fracture after surgery	4	5
G	84	Female	8	23	Right trochanteric fracture after surgery	4	7
H	82	Female	8	23	Left hip fracture after surgery	3	11
Average (SD)	79.5 (8.6)	—	8.6 (1.3)	25 (1.9)	—	2.3 (1.6)	5.6 (3.8)

MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale.

**Figure 1** Course of learning of isometric contraction exercise of the quadriceps. Dashed lines indicate the course of learning in cases A–H, all of whom were postoperative patients without dementia. The patient in this study, whose course is indicated by the blue solid line, took much longer to learn instructions, compared with patients who had good general cognitive function.\* Explanation of figures on the vertical axis:

1: The patient understood the exercise of pushing down on a towel. 2: In addition to 1, the patient explained the number of counts or sets. 3: In addition to 1, the patient explained the numbers of counts and sets.



able to remember this point and answer by rote at the beginning of the next or subsequent sessions.

The 'stair-stepping exercise' required learning to put the legs and a cane on steps. After surgery for hip fracture, it is safer to step stairs with a cane to reduce the load on the operated leg. Therefore, the procedures for stepping stairs were to place the cane, the non-operated leg and the operated leg in order when stepping up; but the cane, the operated leg and the non-operated leg in order when stepping down. Consequently, the non-operated leg always receives the greater load. The patient was asked to remember the order of stepping stairs and after learning this information she could explain the order for stepping up and down by rote at the beginning of the next or subsequent sessions.

Among all the physical therapies for which the patient was asked to remember instructions, it took most time for her to remember the counts when pushing on a towel at the popliteal fossa and the number of repeats in isometric contraction exercise of the quadriceps.

### Comparison of physical therapies that did and did not require time for motor learning

The physical therapies that did and did not require time for motor learning had two differences: the number of issues to keep in mind and familiarity with the motion of the therapy. For example, in 'exercise of legs on the bed', a physical therapy that did not require time for motor learning, the patient was required only to memorise the 'number of exercises' of lifting the legs, rotating the hip joint and extending the hip joint 10 times each. Similarly, the side walk only required remembering 'to keep the toes straight ahead', and in the 'stair-stepping exercise' the patient only had to remember to put the cane and legs down in particular orders when stepping up or down. In addition, these motions were relatively familiar to the patient. Therefore, these were defined here as 'single task' exercises.

In contrast, in the isometric contraction exercise of the quadriceps, which did require time for motor learning, the patient needed to remember both the counts when pushing on the towel at the popliteal fossa and the number of repeated exercise sets, that is, two tasks. Furthermore, the patient was unfamiliar with the motion of pushing down on the towel at the popliteal fossa. Therefore, this exercise was defined here as a 'dual task' exercise.

The patient attained long-term memory in the single task, but the dual task remained in the 'short-term memory' and required much more time to reach the long-term memory (figure 2). Neuropsychological test results and MRI and PET images of the head and were analysed to examine why the patient took much longer to remember the instructions for isometric contraction exercise of the quadriceps, despite the absence of dementia, depression and apathy.

### Examination of frontal lobe function

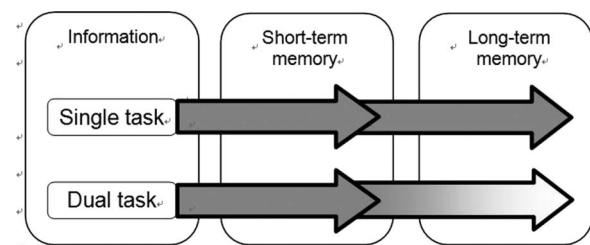
The patient had poor scores for calculations and spelling words backwards in the MMSE. Therefore, frontal lobe function was examined.

#### Digit span

Performance on forward and backward digit span tests is associated with verbal 'short-term memory' and verbal 'working memory,' respectively. In clinical settings, 'short-term memory' in this study was defined as the retention of information in a very short time, whereas 'working memory' was considered to be processing information retained as 'short-term memory.' The mean forward and backward digit span values were  $5.6 \pm 1.1$  and  $4.3 \pm 1.1$ , respectively, in patients aged  $83 \pm 3.6$  years.<sup>10</sup> These were 5 and 2, respectively, in our patient.

#### Visuospatial span

Spatial forward and backward span tests were related to visuospatial short-term and 'working memory,' respectively. The mean spatial forward and backward span values were  $4.8 \pm 0.8$



**Figure 2** Differences in commitment to memory between single and dual tasks. The patient attained long-term memory for a single task, but dual tasks remained in the short-term memory. A much longer period was required to attain long-term memory for the dual task.

and  $4.6 \pm 0.9$ , respectively, in patients aged  $83 \pm 3.6$  years.<sup>10</sup> In our patient, these were 4 and 2.

## Frontal assessment battery

The mean total score is  $13.8 \pm 2.6$  in patients aged  $\geq 80$  years.<sup>11</sup> The score for our patient was 11 out of 18.

## Weigl test

A subject classifies 12 blocks marked with a heart, club, diamond or spade and with differences in size, colour, shape or thickness, using five factors: mark, colour, shape, size and thickness of blocks. The score for each factor ranges from 0 to 3 and the total possible score is 15.<sup>12</sup> This task requires a patient to keep new and previous information in mind, choose appropriate objects or decisions, maintain the set (structure) and change (shift) them in accordance with updated information. The mean total score was  $13.0 \pm 0.0$  in patients aged 70–85 years.<sup>13</sup> The score for our patient was 0 out of 15.

## Trail making test

A previous study showed that the mean times to complete tests A and B were  $73.9 \pm 26.0$  and  $229.1 \pm 94.9$  s, respectively, in patients aged 75–84 years.<sup>14</sup> Our patient completed test A in 52 s, but failed to complete test B due to making many errors in numbers and letters and being unable to revise these errors.

## Imaging findings

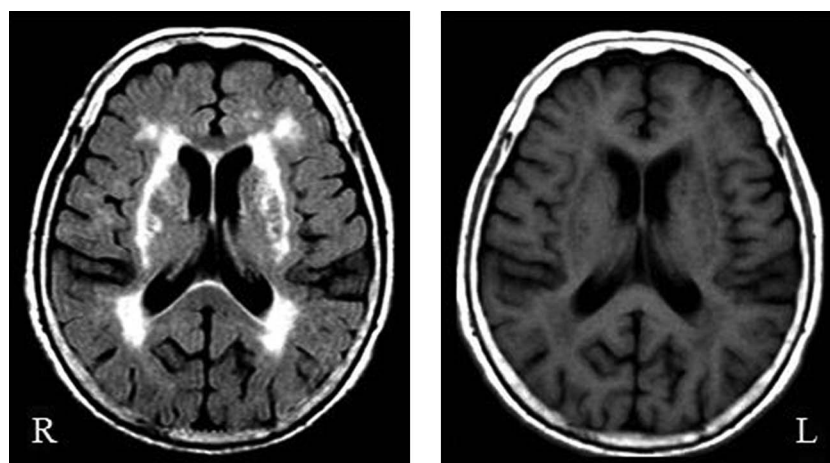
The patient underwent head MRI and FDG-PET to examine brain function. MRI (figure 3) revealed deep white matter changes, but no cerebrovascular lesions were found.

Glucose metabolism in the brain was evaluated with FDG-PET. Three-dimensional stereotactic surface projections were generated using a Z score map (figure 4). The results showed reduced metabolism in the bilateral frontal lobes, and particularly in the dorsolateral prefrontal area, anterior cingulate and orbital area.

## OUTCOME AND FOLLOW-UP

The patient had reduced working memory, and consequently she required a long time to remember instructions for isometric contraction exercise of the quadriceps. The MRI revealed deep white matter changes. The FDG-PET showed reduced metabolism in the bilateral frontal lobes, and particularly in the dorsolateral prefrontal area, anterior cingulate and orbital area. No follow-up data were obtained.

**Figure 3** Head MRI. Fluid-attenuated inversion recovery (left) and T1-weighted (right) images revealed deep white matter changes around the cerebral ventricle, but no cerebrovascular lesions were found.



## DISCUSSION

The patient had reduced frontal lobe function, particularly for 'working memory,' and consequently she required a long time to remember instructions for isometric contraction exercise of the quadriceps, despite the absence of apparent dementia, depression and apathy.

## Limitations in neuropsychological and behavioural assessments

The main question is the inability of the patient to learn 10 repetitions of quadriceps exercise with a 10 s hold. There is enough evidence to prove that in the elderly with decreasing working memory they are able to hold the instructions within their small focus of attention.<sup>15</sup> In *prima facie* it seems the patient had other cognitive domains affected too, which barred her from learning the exercise instructions. Hence the choice of neuropsychological tests is critical. Also, the areas where the lesions have been found play an important role in problem solving, executive memory, abstract thinking, reward anticipation, decision-making, etc. Hence a comprehensive evaluation through appropriate neuropsychological tests was important to strongly correlate the lesion areas and its affection to patient's exercise performance. However, limited time in the rehabilitation ward where many patients should be treated at the same time prevented us from performing such detailed neuropsychological tests. Despite the limitations, we consider that the case could provide an evidence of rehabilitation for dementia.

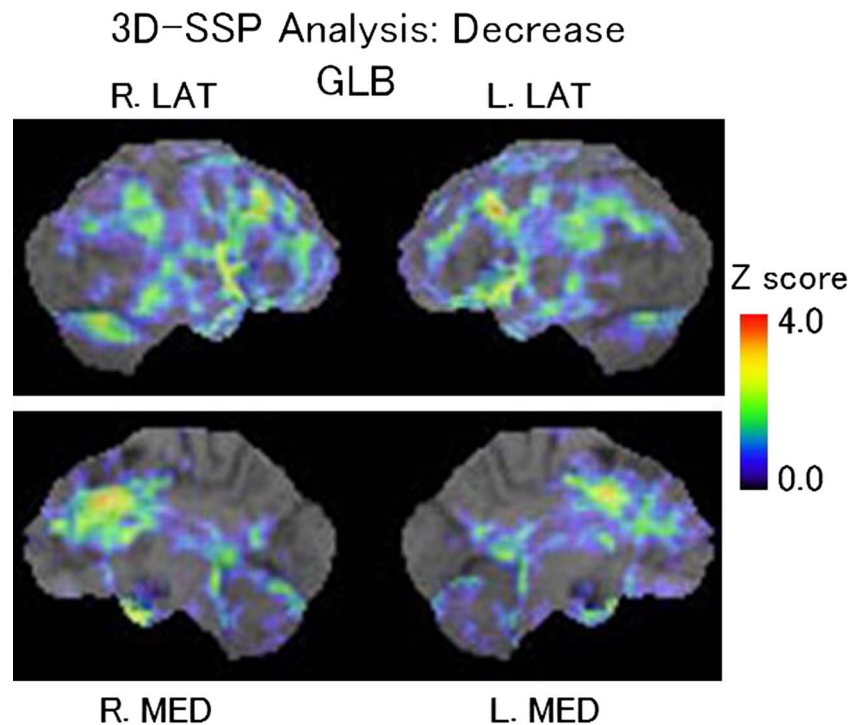
## Comparison with results of previous imaging studies of brain functions

Using functional MRI, the left dorsolateral prefrontal area, the temporal lobe and bilateral cingulate gyrus were found to be activated in the trail making test-B<sup>16</sup> and the bilateral inferior frontal sulcus, supramarginal gyrus and anterior cingulate were activated in the Wisconsin Card Sorting Test.<sup>17</sup> Using PET, the left supplementary motor area and the posterior parietal lobe were found to be activated in verbal 'working memory,' while the right supplementary motor area, posterior parietal lobe and occipital lobe were activated in the visuospatial working memory of Broca's area.<sup>18</sup> These areas and the area with reduced glucose mechanism in the patient are shown in figure 5.

The patient had poor scores in the trail making test B, the Weigl test, for counting forward and for visuospatial backward span. The Weigl test and Wisconsin card sorting test<sup>19</sup> are sorting tests, and therefore the brain area activated in the respective tasks is likely to be similar. As shown in figure 5, the



**Figure 4** Fluorodeoxyglucose positron emission tomography images with a standardised Z score map of the whole brain glucose metabolism was reduced in the bilateral frontal lobes, particularly in the dorsolateral prefrontal area, the anterior cingulate and the orbital area. 3D-SSP, three-dimensional stereotactic surface projections; GLB, global; R.LAT, right lateral; L.LAT, left lateral; R.MED, right medial; L.MED, left medial.



areas with reduced mechanism were similar to the cerebral areas found to be activated in neuropsychological tests, except for the area in the right dorsolateral prefrontal area, which was not explained by the neuropsychological tests.

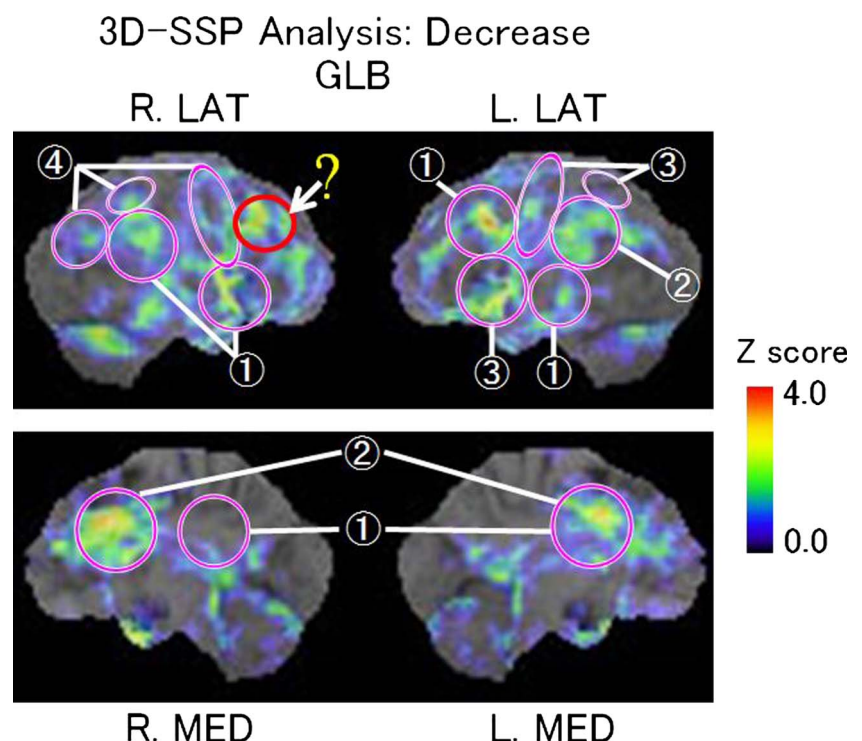
#### Association with 'working memory'

Recent studies suggested that the working memory is involved in retaining new information as long-term memory.<sup>20</sup> In daily life events commonly occur for which information can be easily recalled when we repeat to rehearse the information in our

mind. Studies of phonological working memory by Davachi *et al*<sup>21</sup> and of visuospatial working memory by Ranganath *et al*<sup>20</sup> suggested that maintenance of information in the working memory involves use of long-term memory.

Kondo *et al*<sup>22</sup> classified 20 healthy volunteers into large-working and small-working memory groups: the patients were asked to solve the calculation while keeping the target word in mind (dual task), and then asked to recall the word. The patients with large working memory recalled more words, and functional MRI showed that the anterior cingulate was

**Figure 5** Areas with reduced glucose mechanism in the patient and cerebral areas activated by neuropsychological tests in previous studies. (1) Areas activated in trail making test B to a greater extent than in test A on functional MRI,<sup>16</sup> (2); Areas activated in the Wisconsin Card Sorting Test on functional MRI,<sup>17</sup> (3); Areas activated in the verbal working memory task on positron emission tomography (PET),<sup>18</sup> (4); Areas activated in the visuospatial working memory task on PET.<sup>18</sup> Activation in the right dorsolateral prefrontal area (red circle) could not be explained based on previous results for activation in neuropsychological tests. 3D-SSP, 3D stereotactic surface projections; GLB, global; R.LAT, right lateral; L.LAT, left lateral; R.MED, right medial; L.MED, left medial.



activated. Furthermore, in patients with large working memory, the cingulofrontal network was strongly associated with working memory.

In our patient, FDG-PET showed reduced metabolism in the anterior cingulate, and 'working memory' was also reduced. Therefore, the patient may have received a greater load that overwhelmed the reduced 'working memory' in the dual task of isometric contraction exercise than in the single tasks. She completed the exercise under supervision of a therapist, suggesting that her 'working memory' was sufficient to complete the task, but not enough to transform the instructions into long-term memory. This may explain the longer time required for motor learning.

## Association with deep white matter changes

Head MRI detected no cerebral stroke, but showed white matter changes around the cerebral ventricle. Swartz *et al*<sup>23</sup> found that those with moderate to severe deep white matter changes in the cholinergic neuron network had similar memory and general cognitive function to those with mild changes; however, deep white matter changes were associated with impaired executive function and visuospatial attention and might result in deteriorated attention.<sup>24</sup> Therefore, the deep white matter changes around the cerebral ventricle in our patient might have affected the cingulofrontal network, which is thought to be involved in working memory.<sup>21</sup> This may also partially explain the cause of learning disabilities in patients with dementia.

## Application to rehabilitation therapy

As described above, a key to a successful outcome of rehabilitation therapy is for the patient to learn the exercise procedures. In our case, the patient took longer to learn the exercises, but reached the learning goal in a step-by-step manner. Therefore, when instructing a patient with reduced 'working memory', it might be effective to divide target tasks into simple step-by-step instructions to decrease the amount of information given at one time. In addition, a motion with which a patient is unfamiliar might cause a greater load to be placed on the 'working memory.' Therefore, familiar motions might be more appropriate for physical therapy in patients with apparent dementia.

## Learning points

- ▶ The patient had reduced working memory, and consequently she required a long time to remember instructions for isometric contraction exercise of the quadriceps.
- ▶ The MRI revealed deep white matter changes.
- ▶ The <sup>18</sup>F-fluoro-D-glucose-positron emission tomography showed reduced metabolism in the bilateral frontal lobes, and particularly in the dorsolateral prefrontal area, anterior cingulate and orbital area.

**Contributors** KT is the physical therapist, and KM and MN are the neurologists for the case. NT was involved in writing the article and was the physicist who performed positron emission tomography.

**Competing interests** None.

**Patient consent** Obtained.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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